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NEUTRON EFFECTIVENESS FOR CAUSING INCAPACITATION IN MONKEYS

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ABSTRACT

Fifty-eight male monkeys (Macaca mulatta) were trained by shock avoidance conditioning to work a simultaneous visual discrimination problem. Trained subjects were irradiated in either a nuclear reactor-produced neutron field (incident neutron to gamma ray ratio of about 10) or a similarly produced gamma ray field (incident neutron to gamma ray ratio of about 0.1). In all exposures the midbrain dose rate was about 2000 rads/minute. The midbrain dose most likely to cause early transient incapacitation (ETI) in 50 percent of the irradiated subjects was 2186 $\overset{\times}{\div}$ 1.16 rads in the gamma ray field and 3215 $\overset{\times}{\div}$ 1.25 rads in the neutron field; the relative effectiveness of the neutron field for producing ETI was, therefore, 0.68. The signs and symptoms of ETI were the same whether the monkey received gamma or neutron radiations.

I. INTRODUCTION

It has been established that some degree of early transient incapacitation (ETI) usually occurs in trained monkeys that receive 1500 to 10,000 rads of pulsed mixed gamma-neutron radiation.[5,8] Similarly, ETI occurs after irradiation of trained miniature pigs.[1] For both species the incidence and severity of ETI are directly related to dose. However, in miniature pigs, the head is primarily involved in the ETI response as indicated by partial body irradiation studies[7] and by the fact that signs of severe central nervous system (CNS) damage (convulsions, coma, etc.) are clearly present during ETI. By contrast, convulsions are rarely seen during ETI in monkeys, and the results of partial body irradiation studies[8] indicated that irradiation of either head or trunk structures can produce ETI in monkeys. Gamma irradiation was more effective than neutron irradiation for causing ETI and severe CNS damage in miniature pigs when high dose rates (approximately 2000 rads/minute) were used.[4]

The purpose of this study was to evaluate the relative effectiveness of neutron irradiation for causing ETI in monkeys.

II. PROCEDURE

Fifty-eight male monkeys (Macaca mulatta) that weighed between 3 and 5 kg were used in this study. Each monkey was trained by shock avoidance conditioning to work a simultaneous visual discrimination problem. The monkeys were restrained in primate chairs for the entire period of training, exposure and postexposure testing, generally about 25 days.

The discrimination problem consisted of the simultaneous presentation of a circle and a square on two illuminated keys of a console in front of the monkey.[2] The

relative positions of the circle and square were switched in a random fashion. The correct response was to press the key illuminated with the square.

Each trial lasted 10 seconds. It was initiated by simultaneous illumination of a house light in the testing chamber and the stimulus keys on the console. The monkey had 5 seconds to respond. A correct response extinguished both house light and stimuli for the duration of the 10 seconds. However, for an incorrect response or for no response the stimuli extinguished, the house light remained on, a tone was initiated, and the animal received a brief electrical shock. Before irradiation, each subject was trained to a proficiency of 90 or more correct responses in 100 trials.

The monkeys were irradiated with the AFRRI-TRIGA reactor. Shielding methods described elsewhere[4,9] were used to modify the ratio of neutron to gamma ray tissue kerma, free-in-air, to produce either a "neutron field" or a "gamma ray field". The neutron to gamma ray ratios were approximately 10 and 0.1 for the neutron and gamma ray fields, respectively.

Depth-dose patterns across the brain of a monkey cadaver were measured with miniature tissue-equivalent ionization chambers. Dosimetry was similar to that reported for related research with miniature pigs.[4,9] The dosimetry results are summarized in Table I.

Trained monkeys were irradiated individually with the reactor operated in the steady-state mode. Each subject sat upright and faced away from the reactor core with its center line about 100 cm from the core vertical center line. As in the miniature pig study,[4] the dose rate at the midline of the brain was approximately 2000 rads/minute for all exposures (the highest practical rate attainable for the neutron

Table I. Results of Dosimetry in Monkey Cadaver

Probe location	Percent of midbrain dose		Neutron to gamma ratio* in neutron field
	Gamma ray field	Neutron field	
Head entrance (posterior)	107	117	9
Midbrain	100	100	8
Head exit (anterior)	71	45	5.7
Midthorax	82	58	4.3

* Determined by methods described by Shosa[6]

field). Each irradiation was monitored with miniature ion chambers and sulfur pellets. Irradiation and testing were initiated simultaneously. The monkeys were tested continuously for approximately 600 trials.

To achieve the objective of this research, the ED_{50} of the neutron field was compared to the ED_{50} of the gamma ray field. ED_{50} is defined as the most probable dose that would cause 50 percent of the animals to experience ETI. The "up-and-down" design or "Bruceton" method[3] was used for this evaluation. For this experimental design, the midline tissue doses to the brain were 1600, 1800, 2100, 2400, and 2700 rads for the gamma ray field and 2200, 2500, 2900, 3300, 3800, and 4400 rads for the neutron field.

The occurrence of ETI was considered as a yes or no response rather than a graded response. Therefore, data from earlier studies[5,8] were compiled and reviewed to decide what constitutes ETI and to estimate the best doses to use in the experimental design of this study. It was decided that any subject with three or more consecutive omissions during the first 30 minutes after the onset of irradiation would be considered to have experienced ETI.

III. RESULTS

The doses used and the performance of irradiated animals are summarized in Tables II and III. There was no apparent difference between the ETI observed after

Table II. Performance of Neutron-Irradiated Monkeys

Dose group allotment* † (rads)‡						Postirradiation performance			Midbrain dose (rads)‡
2200	2500	2900	3300	3800	4400	Correct	Incorrect	Omission	
		+				581	7	13	2700
			+			584	14	2	3400
				0		525	16	59	3800
			+			592	1	7	3300
				0		576	4	27	3800
			+			594	1	5	3100
				0		447	1	152	3900
			0			551	20	30	3400
		+				594	2	4	3000
			+			601	1	6	3300
				+		592	2	7	3800
					0	20	1	579	4200
				0		389	4	207	3700
			0			274	61	266	3300
		0				575	2	24	2900
	+					589	4	7	2600
		+				574	17	9	2800
			+			591	4	5	3200
				0		485	1	114	3900
			0			563	24	14	3300
		0				403	19	178	3000
	+					584	6	10	2600
		0				561	29	10	3000
	0					305	4	291	2600
+						590	4	6	2100
	+					572	3	26	2600
		+				293	3	4	3100
			+			392	0	8	3300

* Each succeeding animal was tested at the dose level one step below the dose used in the preceding test if it resulted in ETI, or at the dose level one step higher if performance was satisfactory.

† Satisfactory performance is indicated by "+", ETI is indicated by "0".

‡ The midbrain dose reported is the dose derived from measurements during the exposure. The "dose group" to which an animal was assigned indicated the dose the animal should have received according to experimental design. The dose measurements have an estimated accuracy of better than $\pm$ 5 percent.

Table III. Performance of Gamma-Irradiated Monkeys

Dose group allotment*† (rads)‡					Postirradiation performance			Midbrain dose (rads)‡
1600	1800	2100	2400	2700	Correct	Incorrect	Omission	
	+				583	9	8	1700
			0		502	7	91	2400
		0			545	1	55	2000
	+				595	0	5	1900
		0			276	4	24	2200
	+				590	2	8	1900
		+			546	0	58	2000
			0		558	8	34	2400
		0			591	3	6	2200
	+				598	1	1	1900
		+			597	3	0	2100
			+		494	20	26	2400
				0	563	4	33	2600
			+		535	2	3	2400
				0	565	7	28	2600
			0		465	11	124	2500
		0			589	1	10	1900
	0				542	6	52	1800
+					574	20	6	1700
	+				594	0	6	1900
		0			391	16	93	2100
	+				572	28	0	1900
		+			588	3	9	2300
			0		186	25	389	2500
		+			560	34	6	2300
			0		563	1	36	2500
		+			394	1	6	2300
			0		514	1	36	2400
		+			583	12	5	2100
			0		19	1	380	2300

* Each succeeding animal was tested at the dose level one step below the dose used in the preceding test if it resulted in ETI, or at the dose level one step higher if performance was satisfactory except for the second animal.

† Satisfactory performance is indicated by "+", ETI is indicated by "0".

‡ The midbrain dose reported is the dose derived from measurements during the exposure. The "dose group" to which an animal was assigned indicated the dose the animal should have received according to experimental design. The dose measurements have an estimated accuracy of better than $\pm$ 5 percent.

gamma ray exposures and that which occurred in the neutron field. For both types of irradiation, the ETI was similar to that described earlier for a mixed gamma-neutron field (incident neutron to gamma ray ratio of about 0.4).[5,8] Among the neutron-irradiated animals, the lowest dose at which ETI occurred was 2600 rads, and that was in only one of four monkeys (Table II). By contrast, ETI occurred in one monkey at a gamma ray dose of 1800 rads, and ETI always occurred in monkeys that received more than 2500 rads in the gamma ray field (Table III).

From the data presented, it was calculated that the ED_{50} for the gamma ray field was 2186 $\overset{\times}{\div}$ 1.16 rads (midline tissue dose to the brain), and the ED_{50} for the neutron field was 3215 $\overset{\times}{\div}$ 1.25 rads (Table IV). With a confidence of 95 percent the gamma ray field ED_{50} was within the range of 2028 to 2356 rads while the neutron field ED_{50} was within the range of 2867 to 3606 rads. The difference between the two ED_{50}'s was highly significant ($p < 0.01$). The relative effectiveness of the neutron field for causing ETI (gamma ED_{50} ÷ neutron ED_{50}) at the ED_{50} point was 0.68. All calculations were based upon the logarithm of dose versus response.*

Table IV. Results of Data Analysis of Neutron and Gamma Ray Exposures with Monkeys (based upon midbrain doses)

	Gamma ray field (rads)	Neutron field (rads)
ED_{50}	2186 $\overset{\times}{\div}$ 1.16	3215 $\overset{\times}{\div}$ 1.25
95% confidence limits		
Lower	2028	2867
Upper	2356	3606

* Statistical analyses accomplished by S. G. Levin, mathematical statistician, Head, Mathematical Analysis Division, Physical Sciences Department.

IV. DISCUSSION

To elicit ETI in trained monkeys, significantly higher midbrain doses were required in the neutron field than in the gamma ray field. Therefore, it was concluded that gamma irradiation was much more effective than neutron irradiation for causing ETI as defined in this study. The ED_{50} for causing ETI with pulsed mixed gamma-neutron radiation was estimated to be about 2200 rads in results published earlier.[5,8] The incident neutron to gamma ray ratio under those conditions was about 0.4. Although the irradiation conditions were somewhat different for the earlier studies, the results tend to support the conclusion that gamma rays are more effective than neutrons for causing ETI.

It has been shown that irradiation of either head or trunk structures can produce ETI in monkeys, with head structures being more important than the rest of the body.[8] By using the factors 0.58 and 0.82 as appropriate (Table I), the midthorax doses at the ED_{50} and 95 percent confidence limits were calculated (Table V). The ED_{50} midthorax doses were approximately equal, but they were much lower than either the associated

Table V. Midthorax Doses for ED_{50} and 95 Percent Confidence Limits

	Gamma ray field (0.82* x midbrain dose†) (rads)	Neutron field (0.58* x midbrain dose†) (rads)
ED_{50}	1792	1864
95% confidence limits		
Lower	1662	1662
Upper	1931	2091

* Table I
† Table IV

midbrain doses or the 2200-rad dose estimated to be the ED_{50} for whole-body exposures with pulsed mixed gamma-neutron radiation.[5,8] Therefore, for the current study, it was concluded that doses to the thorax were far less important than those to the head for causing ETI. For that reason, it was concluded also that the difference in relative effectiveness of neutrons as compared to gamma rays for causing ETI must reflect some difference between the two types of irradiation in their ability to disrupt the CNS.

It is not clear why gamma rays should have a greater effect than neutrons upon the CNS. However, it is postulated that much of the absorbed energy from neutron-produced high linear energy transfer (LET) particles is "wasted"; a more thorough discussion of this concept can be found in an earlier report.[4]

The relative effectiveness of neutrons for causing ETI was much lower for miniature pigs (0.23)[4] than for monkeys (0.68). Before discussing reasons for the difference, it is important to recognize that the end points of performance changes were somewhat subjectively established in both cases. Other observers, by using different end points or different means of determining the end points, might have found either larger or smaller differences between the response of monkeys as compared to that of miniature pigs. The fact that the value for neutron relative effectiveness was significantly less than one in both monkey and miniature pig experiments supports the conclusion that gamma rays are more effective than neutrons for causing early postirradiation CNS disturbances.

If the values for relative neutron effectiveness are truly different for the two species, there are at least two possible reasons for the difference. One possibility

is that the mechanism of ETI is different in miniature pigs than in monkeys. As mentioned earlier, primary involvement of head structures and CNS damage in ETI has been more clearly demonstrated for the pig[1,7] than for the monkey.[5,8] Another possible reason for the difference is that dose rate factors could have been more important for the miniature pigs[4] than for the monkeys. In both studies, the mid-brain dose rate was 2000 rads/minute. However, the range of total exposure times was from less than 1 to greater than 9 minutes for the pigs compared to a range of exposure times that generally fell between 1 and 2 minutes for monkeys. It is not clear how these and other factors interrelate to cause the apparent differences between monkeys and miniature pigs, but they should provide fruitful areas for research to explain the differences.

There is one other unexplained difference between the response observed in miniature pigs and that observed in monkeys. Convulsions and coma as evidence of CNS involvement were much more frequent in gamma-irradiated pigs than in neutron-irradiated pigs. There was no apparent difference between the type of ETI observed in gamma-irradiated monkeys and that observed in neutron-irradiated monkeys. Neither group of monkeys appeared to experience convulsions or other obvious signs of severe CNS damage.

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13. ABSTRACT

Fifty-eight male monkeys (Macaca mulatta) were trained by shock avoidance conditioning to work a simultaneous visual discrimination problem. Trained subjects were irradiated in either a nuclear reactor-produced neutron field (incident neutron to gamma ray ratio of about 10) or a similarly produced gamma ray field (incident neutron to gamma ray ratio of about 0.1). In all exposures the midbrain dose rate was about 2000 rads/minute. The midbrain dose most likely to cause early transient incapacitation (ETI) in 50 percent of the irradiated subjects was 2186 $\times\div$ 1.16 rads in the gamma ray field and 3215 $\times\div$ 1.25 rads in the neutron field; the relative effectiveness of the neutron field for producing ETI was, therefore, 0.68. The signs and symptoms of ETI were the same whether the monkey received gamma or neutron radiations.

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